PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 280/761/PWO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2005/000566	International filing date *(day/month/year)* 17.02.2005	Priority date *(day/month/year)* 17.02.2004
International Patent Classification (IPC) or national classification and IPC INV. A61L15/60 A61L17/06 A61L27/22 A61L15/32		
Applicant ADVANCED PROTEIN SYSTEMS LIMITED		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☒ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand 15.12.2005	Date of completion of this report 19.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Menidjel, R Telephone No. +31 70 340-3680

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2005/000566

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

   ☐ international search (under Rules 12.3 and 23.1(b))
   ☐ publication of the international application (under Rule 12.4)
   ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-38 as originally filed

Claims, Numbers

1-63 filed with telefax on 15.12.2005

Drawings, Sheets

1/1 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages
   ☐ the claims, Nos.
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

   ☐ the description, pages
   ☒ the claims, Nos. 30,32,33-36 (all in part), 37, 39-53 (all in part), 57-63 (all in part)
   ☐ the drawings, sheets/figs
   ☐ the sequence listing *(specify)*:
   ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 42-45,47,51-53,57-63 (all in part)

because:

☒ the said international application, or the said claims Nos. 42-45,47,51-53,57-63 (all in part) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-29,33-36 (all in part), 38,39-41 (all in part), 46 (in part), 48-53 (all in part), 54-56, 57-63 (all in part)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-29,33-36 (all in part), 38,39-41 (all in part), 46 (in part), 48-53 (all in part), 54-56, 57-63 (all in part)
Industrial applicability (IA)	Yes:	Claims	1-29,33-36 (all in part), 38,39-41 (all in part), 46 (in part), 48-50 (all in part), 54-56
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

- The subject-matter of claims 42-45,47,51-53,57-63 (all in part) is related to a method for treatment of the human or animal body from surgery or therapy. Using its discretion, the present authority decided not to carry out an internal preliminary examination on that subject-matter (Article 34(4)(a) PCT in conjunction with Rule 67.1(iv) PCT).
For the assessment of the present claims 42-45,47,51-53,57-63 (all in part) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- The amendments filed by the applicant do introduce subject-matter which extends beyond the content of the application as filed according to Article 34(2)(b) PCT for the following reasons:
Present claims 30 and 37 refer to a method of forming a protein polymer and a protein polymer "...such that the dicarboxylic acid or activated derivative thereof forms a spacer in which the carboxyl groups are reacted directly with groups in the protein molecules." There is no basis in the application as filed for such amendment.

1 - The following documents (D1-D4) are referred to in this communication (Article 33(6) PCT); the numbering will be adhered to in the rest of the procedure:
D1: US-A-5 733 563 (FORTIER ET AL) 31 March 1998 (1998-03-31)
D2: US 2003/211137 A1 (SIERRA DAVID) 13 November 2003 (2003-11-13)
D3: US-A-5 412 076 (GAGNIEU ET AL) 2 May 1995 (1995-05-02)
D4: EP-A-0 807 441 (NYCOMED IMAGING AS) 19 November 1997 (1997-11-19)

2. Novelty (Article 33(2) PCT)

- The subject-matter of present claims 1-29,33-36 (all in part),38,39-41 (all in part),46 (in part),48-53 (all in part),54-56,57-63 (all in part) is considered as novel over the cited prior art for the following reasons (Article 33(2) PCT):

- Document D1 (US5733563) describes a bioartificial hydrogel comprising a bifunctionalized polyethylene oxide, activated with an activating agent, and an **albumin** type protein. The bioartificial hydrogel may be used as dressing (Cf. D1, column 1, lines 10-16; column 4, lines 18-30; column 8, lines 54-60; claims 1-5,12).

- Document D2 (US2003211137) refers to a method of forming a **wound dressing** by reacting a protein polymer such as **albumin** with a **polyfunctional spacer** or an activated derivative thereof (Cf. D2, page 1, paragraph 11; page 1, paragraph 17-page 2, paragraph 19; page 3, paragraph 32; page 3, paragraph 34-paragraph 37; claims 1-28).

- Document D3 (US5412076) describes a method of forming a protein polymer such as **collagen** by reacting a protein with a **dicarboxylic acid** or an activated derivative thereof (Cf. D3, column 1, lines 35-53; column 2, lines 21-48; column 4, lines 11-36; column 5, line 66-column 10, line 44; examples 10,11).

- Document D4 (EP0807441) describes a contrast agent for use in diagnostic comprising a protein polymer such as human serum albumin crosslinked with a biodegradable linkage selected from amide, imide, imine, ester etc. (Cf. D4, column 3, line 31-column 4, line 6; column 4, lines 30-56; column 5, lines 40-46; claims 1-15).

- None of the cited document refer to a method of forming a wound dressing which method comprises forming a protein polymer such as albumin by reacting with a polyfunctional spacer or an activated derivative thereof, wherein the spacer is selected from the group consisting of polycarboxylic acids, polyamines, poly(carboxy/amino) compounds, polyalcohols, polyketones, polyaldehydes and polyesters.

3. Inventive Step (Article 33(1),(3) PCT)

- Although novel, the subject-matter of present claims 1-29,33-36 (all in part),38,39-41 (all in part),46 (in part),48-53 (all in part),54-56,57-63 (all in part) cannot be considered as being inventive for the following reasons (Article 33(1),(3) PCT):

- The problem to be solved by the present application is to provide a **protein polymer gel** suitable for topical administration as **wound dressings.**

- The solution proposed in the present application is method of forming a wound dressing, which method comprises forming a **protein polymer** by reacting a protein with a polyfunctional spacer as described in present claim 1.

- Document D2 (US2003211137), which is considered as the closest prior art, refers to a method of forming a **wound dressing** by reacting a **protein polymer** with a **polyfunctional spacer** or an activated derivative thereof.

- The difference between the teaching of the closest prior art and the subject-matter of present claims 1-29,33-36 (all in part),38,39-41 (all in part),46 (in part),48-53 (all in part),54-56,57-63 (all in part) is merely the choice of specific spacers.

- The features described in present claims 1-29,33-36 (all in part),38,39-41 (all in part),46 (in part),48-53 (all in part),54-56,57-63 (all in part) are merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.
Therefore, the subject-matter of present claims 1-29,33-36 (all in part),38,39-41 (all in part),46 (in part),48-53 (all in part),54-56,57-63 is not considered as being inventive according to Article 33(1),(3) PCT.

- Claims 42-45,47,51-53,57-63 (all in part) relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

4. Industrial Application (Article 33(4) PCT)

- The subject-matter of present claims 1-29,33-36 (all in part),38,39-41 (all in part),46 (in part),48-50 (all in part),54-56 is considered to be industrially applicable; claims 1-29,33-36 (all in part),38,39-41 (all in part),46 (in part),48-50 (all in part),54-56 therefore, satisfy the criterion set forth in Article 33(4) PCT.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.

PCT/GB2005/000566

Re Item VI

Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2005/063311	14.07.2005	30.11.2004	26.12.2003

Although WO2005/063311 does not constitute prior art within the meaning of Rule 64.1(b) PCT, it appears to be particularly relevant in regard to the subject-matter of claims 1,3-8,14,15,18,21,22,24-29. No check has been maid has to whether the priority of the present application have been validly claimed.

Claims

1. A method of forming a wound dressing, which method comprises forming a protein polymer by reacting a protein with a polyfunctional spacer, or an activated derivative thereof, wherein the spacer is selected from the group consisting of polycarboxylic acids, polyamines, poly(carboxy/amino) compounds, polyalcohols, polyketones, polyaldehydes and polyesters.

2. A method as claimed in Claim 1, wherein the protein polymer is formed *in situ*.

3. A method as claimed in Claim 1, wherein the protein polymer is formed prior to application.

4. A method as claimed in Claim 3, wherein a supporting substrate is incorporated into the dressing.

5. A method as claimed in Claim 3 or 4, wherein the dressing is in the form of a bandage or gel sheet.

6. A method as claimed in any preceding claim, further comprising the application to the wound dressing of a vapour-permeable membrane.

7. A method as claimed in any preceding claim, wherein the protein is a globular protein.

8. A method as claimed in any one of Claims 1 to 6, wherein the protein is a fibrous protein.

9. A method as claimed in Claim 7, wherein the globular protein is a serum protein.

10. A method as claimed in Claim 9, wherein the protein is albumin.

11. A method as claimed in Claim 10, wherein the albumin is human serum albumin.

12. A method as claimed in Claim 1, wherein the protein is blood-derived.

13. A method as claimed in Claim 1, wherein the protein is a recombinant product.

14. A method as claimed in any preceding claim, wherein the spacer is selected from the group consisting of polycarboxylic acids, polyamines and poly(carboxy/amino) compounds.

15. A method or wound dressing as claimed in Claim 14, wherein the spacer is a polycarboxylic acid.

16. A method as claimed in Claim 15, wherein the polycarboxylic acid is a dicarboxylic acid.

17. A method as claimed in Claim 16, wherein the dicarboxylic acid is an alkylene dicarboxylic acid.

18. A method as claimed in any preceding claim, wherein the spacer is activated to facilitate reaction with the protein molecules.

19. A method as claimed in Claim 18, wherein the activating agent is a carbodiimide compound.

20. A method as claimed in Claim 19, wherein the carbodiimide compound is ethyl[dimethylaminopropyl]-carbodiimide.

21. A wound dressing prepared by the method of any preceding claim.

22. A wound dressing comprising a protein polymer formed by reacting a protein with a polyfunctional spacer, or an activated derivative thereof,

wherein the spacer is selected from the group consisting of polycarboxylic acids, polyamines, poly(carboxy/amino) compounds, polyalcohols, polyketones, polyaldehydes and polyesters.

23. A wound dressing as claimed in Claim 22, which is formed *in situ*, by reaction of the protein and polyfunctional spacer, or activated derivative thereof, at the wound site.

24. A wound dressing as claimed in Claim 22, which is preformed, prior to application of the dressing to the wound site.

25. A wound dressing as claimed in Claim 24, which comprises a bandage impregnated with the protein polymer.

26. A wound dressing as claimed in Claim 24, which is in the form of a gel sheet.

27. A wound dressing as claimed in Claim 25, in which the gel sheet has a supporting substrate.

28. A wound dressing as claimed in any one of Claims 21 to 27, which further comprises one or more therapeutically active agents.

29. A wound dressing as claimed in Claim 28, wherein the therapeutically active agents are selected from the group consisting of antibiotics, antivirals, anti-inflammatory agents, pain killers, haemostatic agents, phages, growth factors, anti-scarring agents, odour-absorbing agents, and agents that promote angiogenesis.

30. A method of forming a protein polymer, which method comprises reacting protein molecules with an alkylene dicarboxylic acid or an activated derivative thereof, provided that the protein is not bovine serum albumin, such that the dicarboxylic acid or activated derivative thereof forms a spacer in

which the carboxyl groups are reacted directly with groups in the protein molecules.

31. A method of forming a protein polymer, which method comprises reacting albumin with an alkylene dicarboxylic acid or an activated derivative thereof.

32. A method as claimed in Claim 30, wherein the protein is an albumin.

33. A method as claimed in Claim 31 or Claim 32, wherein the protein is human serum albumin.

34. A method as claimed in any one of Claims 30 to 33, wherein the dicarboxylic acid has the formula

$$HOOC(CH_2)_nCOOH$$

in which n is from 1 to 20, preferably from 2 to 12, and more preferably from 3 to 8.

35. A method as claimed in any one of Claims 30 to 34, wherein the dicarboxylic acid is activated with a carbodiimide activating agent.

36. A method as claimed in Claim 35, wherein the activating agent is ethyl[dimethylaminopropyl]-carbodiimide.

37. A protein polymer formed by reacting protein molecules with an alkylene dicarboxylic acid or an activated derivative thereof, provided that the protein is not bovine serum albumin, such that the dicarboxylic acid or activated derivative thereof forms a spacer in which the carboxyl groups are reacted directly with groups in the protein molecules.

38. A protein polymer formed by reacting albumin with an alkylene dicarboxylic acid or an activated derivative thereof.

39. A protein polymer as claimed in Claim 37 or Claim 38, which is in the form of a solution.

40. A protein polymer as claimed in Claim 37 or Claim 38, which is in the form of insoluble particles.

41. A protein polymer as claimed in Claim 37 or Claim 38, which is in the form of a gel.

42. A use of a protein polymer as claimed in any one of Claims 37 to 41 in the delivery of one or more therapeutically active components to the body.

43. A use of a protein polymer as claimed in Claim 41 in the topical treatment of a wound, burn or ulcer.

44. A use as claimed in Claim 43, wherein the protein polymer is applied to the wound, burn or ulcer as a preformed gel.

45. The use as claimed in Claim 43, wherein a protein and a dicarboxylic acid spacer are applied in solution to the wound, burn or ulcer, and the protein polymer is formed *in situ*.

46. The use of a protein polymer as claimed in Claim 37 or Claim 38 as a coating for a device to be implanted in the body.

47. The use of a protein polymer as claimed in Claim 39 as a platelet substitute or platelet enhancer.

48. A protein polymer as claimed in Claim 39, wherein the protein polymer is conjugated with one or more clotting agents or active peptide derivatives.

49. A protein polymer as claimed in Claim 48, wherein the protein polymer is conjugated with fibrinogen.

50. A protein polymer as claimed in Claim 39, which polymer is conjugated to a therapeutically active agent, or a precursor thereof, and to a targeting moiety having an affinity with a specific locus within the body.

51. The use of a conjugate as claimed in Claim 50 in targeted anti-cancer therapies.

52. A protein polymer as claimed in Claim 39, which polymer is conjugated to a contrast agent and to a targeting moiety having an affinity with a specific locus within the body.

53. The use of a conjugate as claimed in Claim 39 in medical imaging applications.

54. A kit for the preparation of a wound dressing according to Claim 21 or Claim 22, which kit comprises a first composition and a second composition, the first composition and the second composition being held in separate containers such that reaction between the first composition and the second composition is prevented.

55. A kit as claimed in Claim 54, wherein the first composition comprises the protein and the polyfunctional spacer, and the second composition comprises an activator for the polyfunctional spacer.

56. A kit as claimed in Claim 55, wherein the first composition is a solution and the second composition is a powder.

57. A method of treatment of the human or animal body, which method comprises the administration to the body of a protein polymer as claimed in any one of Claims 37 to 41.

58. A method as claimed in Claim 57, wherein the protein polymer is administered intravenously.

59. A method as claimed in Claim 57, wherein the protein polymer is administered topically.

60. A method as claimed in any one of Claims 57 to 59, wherein the protein polymer is administered in the form of a solution.

61. A method as claimed in Claim 59, wherein the protein polymer is administered in the form of a powder.

62. A method as claimed in Claim 59, wherein the protein polymer is administered in the form of a gel.

63. A method as claimed in Claim 59, wherein the protein and the dicarboxylic acid cross-linking agent are administered to the body, such that the protein polymer is formed *in situ*.